

- Impressions*
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Looking at the matter from the point of view of the

BY

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HARVEY CUSHING

John A. Cunningham

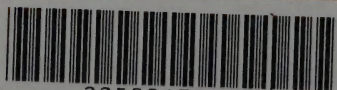
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These six papers provided the basis of the
WILLIAM HENRY WELCH LECTURE

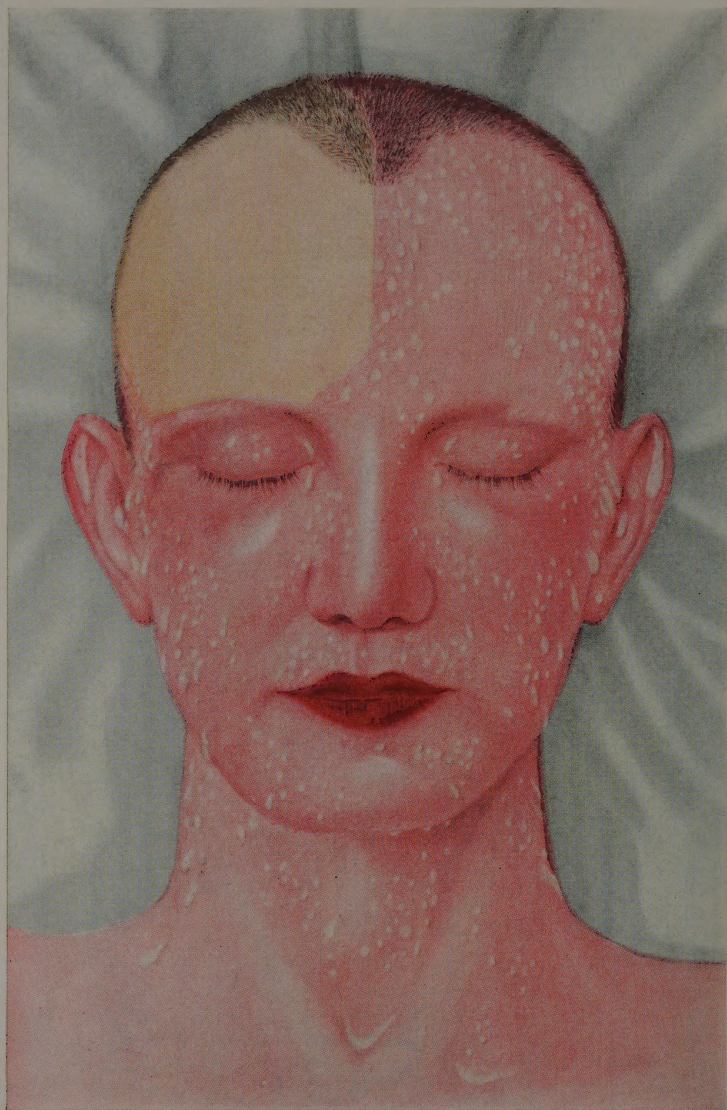
*The Posterior Pituitary Hormone and the
Parasympathetic Nervous System.*

Delivered at the Mount Sinai Hospital, New York
April 30, 1931

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Showing the vaso-dilator and sudorific effects (sparing the bone flap) of 2.5 milligrams of pilocarpine injected into the cerebral ventricles; an intraventricular injection of a cubic centimeter of pituitrin gives the same response.

I. THE REACTION TO POSTERIOR PITUITARY EXTRACT (PITUITRIN) WHEN INTRODUCED INTO THE CEREBRAL VENTRICLES*

BY HARVEY CUSHING

PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL

Communicated March 16, 1931

Introduction.—In 1908,¹ P. T. Herring first clearly described the peculiar hyaline bodies often seen in sections of the neuro-hypophysis and expressed the belief that they represented the secretory product of the epithelial investment of the posterior lobe known as the pars intermedia. The globules appeared to find their way toward the tuber cinereum and in favorable histological preparations could be seen passing between the bodies of the ependymal cells to enter the infundibular cavity.

Two years later (1910), Cushing and Goetsch,² in support of Herring's postulation, supplied experimental evidence in two directions: (1) by showing how occlusion of the pituitary stalk served to dam back the secretory product in the pars nervosa; and (2) by demonstrating, however inconclusively, that the active principle of the lobe was detectable in the cerebrospinal fluid, their deductions having been based on the haemodynamic, peristaltic and diuretic responses to concentrated human ventricular fluids injected for the most part intravenously into rabbits.

From the *histological side* Herring's discovery has received abundant substantiation, though interpretations regarding the source of origin and destination of the hyaline bodies have varied. It is evident that the cells of the pars intermedia et tuberalis, under some nervous stimulus, discharge their ripened cytoplasm into the pars nervosa and that the extruded product undergoes hyalinoid transformation during its migration upward, toward and into the tuberal projection of the diencephalon. Indeed,

* Although the attention of physiologists and pharmacologists was first called to the pituitary body by the discovery of the haemodynamic and diuretic properties found in extracts of its posterior lobe, the function of this obviously important portion of the gland has remained a physiological mystery. One of my anatomist friends who has made notable contributions to our knowledge of the anterior lobe hormones has challenged me to produce any corresponding clinical or experimental evidence of posterior lobe activity. To this challenge this and the succeeding papers are a partial answer.

under certain circumstances large numbers of apparently intact cells, for they still contain recognizable nuclei, may actually thus migrate from its epithelial investment into the substance of the pars nervosa in their passage through which they subsequently become hyalinized.*

This casting off of the cytoplasm in mass or actual discharge of the entire cell body are by no means unique modes of secretion of glandular cells.** What is more, the process, as we know now, is unquestionably under the direct control of certain nerve centers in the interbrain. The presence of a large number of non-myelinated nerve fibers in the neurohypophysis, apparently first observed by Ramon y Cajal in immature mice (1894), was subsequently confirmed by his pupil, Tello³ (1912), for the human gland. It, however, was not until the papers of Pines⁴ (1925) and of Greving⁵ (1926) that the diencephalic centers, from which the fibres take their origin, and their amazingly rich arborization in the posterior lobe came to be fully appreciated and was brought to the attention of physiologists and clinicians.

The interstitial passage of the hyaline bodies through the neurohypophysis and its stalk toward the tuber has meanwhile been observed by many. Edinger⁶ injected the posterior lobe with india-ink and though the mass tended to spread in the direction of the tuber, it did not enter the ventricle. Herring, however, as did Cushing and Goetsch, gave photomicrographs showing hyaline globules actually caught in the process of their extrusion into the ventricle, an observation which has been confirmed among others by Hines,⁷ by da Costa,⁸ by Espino,⁹ and by Remy Collin.^{10,11,12}

From the physiological side, though the conclusions drawn from their early experiments by Cushing and Goetsch met with criticism,¹³ the unmistakable presence in the fluid of a substance, which if not the active principle at least possesses similar properties, has since been clearly demonstrated by a number of workers who have taken advantage of the more exact and dependable oxytocic and melanophore-expanding properties of the extract subsequently discovered by Dale and by Hogben. Thus Cow¹⁴ (1915), Dixon¹⁵ (1923), Trendelenburg¹⁶ (1924), Jánossy and Horváth¹⁷ (1925), Miura¹⁸ (1925), Trendelenburg¹⁸ (1926), Blau and Hancher¹⁹ (1926), Mestrezat and v. Cauaert²⁰ (1926), McLean²¹ (1928), Hoff and Wermer²² (1928), and Karplus and Peczenik²³ (1930), have

* A photomicrograph illustrating such a cellular migration was given in the author's monograph on the pituitary body, 1912, page 199.

** The three methods of secretory discharge which histologists now recognize are: (1) *merocrine*, in which the secretory granules are periodically extruded without particular change of form in the cell, as in salivary, gastric or anterior pituitary glands; (2) *holocrine*, in which the entire cell body is cast off, as in the sebaceous glands; (3) *apocrine*, in which the ripened cytoplasm is disgorged, as in mammary secretion and in the case of certain cutaneous glands, particularly of the lower animals.

successively shown: (1) that a substance, whose pharmacological properties resemble those of posterior lobe extract,* is often demonstrable in normal ventricular and cisternal though not in the lumbar fluids;²⁰ (2) that it may be augmented by the administration of certain organic extracts¹⁵ as well as by certain drugs particularly those producing diuresis;²² (3) that it disappears after hypophysectomy or occlusion of the pituitary stalk;¹⁶ (4) that it is increased by emotional stimuli;²² and finally (5) that it is augmented by direct electrical stimulation of the hypothalamus or tuber.²³

McLean²¹ in the writer's laboratory was led to believe that the active principle is detectable in the jugular vein in larger amounts than in the cerebrospinal fluid. He consequently concluded that it was initially absorbed solely by the vascular route (the abundant "portal circulation" connecting hypophysis and hypothalamus recently described by Popa and Fielding²⁴ would readily make this possible), and that, being a readily dialysable substance, it found its way into the cerebrospinal fluid through the choroid plexuses. On the other hand, the recent brilliant demonstration of Karplus and Peczenik,²³ who showed that the amount of the oxytocic and melanophore-expanding substance in the fluid is increased by electrical stimulation of the tuber, amply justifies their conservative conclusion that the active principle of the posterior lobe is discharged, at least in part, into the ventricular fluid.

It was the original assumption of Goetsch and Cushing that the extrusion of the hyaline bodies between the ependymal cells into the infundibular cavity, whence they were swept along by the cilia of the ependymal cells until dissolved, represented a form of "external secretion" which, in its cerebrospinal fluid medium, was destined ultimately to reach the blood stream by way of the arachnoid villi. It did not occur to them that the substance owing to its ready diffusability might, by resorption, act directly upon subependymal nerve centers in the walls of the third ventricle. Indeed, twenty years ago little was known of these hypothalamic nerve centers, and the functional importance of the diencephalon was scarcely suspected.

Intravenous Versus Intraventricular Effects of Pituitrin.—When injected intramuscularly or intravenously, in addition to its well-known anti-diuretic effect pituitrin causes prompt blanching of the skin and mucous membranes from a vigorous vaso-constrictor action, dryness of the mouth

* It should be mentioned that Van Dyke, Bailey and Bucy (*J. Pharmacol. & Exper. Therap.*, 1929, 36, 595-610) after a painstaking chemical study have come to the conclusion that the oxytocic and melanophore-expanding effects of cerebrospinal fluids are wholly ascribable to differences in the calcium concentration between the test fluids and the bathing fluids. They have made a strong case but it would be difficult to believe, for example, that an increase in the oxytocic and melanophore-expanding properties of the fluid after electrical stimulation of the tuber could be due to increase of calcium.

from loss of salivary secretion, and an early evacuation due to stimulation of the lower bowel. That injection of the extract directly into the cerebral ventricles calls forth a wholly different response was briefly reported in a recent address dealing in general with what were called neurohypophysial mechanisms.²⁵ It was there stated that the extract thus injected will in certain cases cause an astonishingly prompt response characterized by intense flushing from vaso-dilatation, by profuse perspiration, by retching and vomiting, by salivation, by a marked fall in body temperature, and by a coincidental lowering of the basal metabolic rate. These responses occur in the absence of any significant pupillary change, pilomotor reaction, or stimulation of the lower bowel.

Though the intensity of the reaction varies considerably from case to case, the following protocol may serve as an illustration of a moderately pronounced effect:

The patient, a vigorous young man with outspoken acromegalic gigantism, was admitted to the hospital on December 8, 1930, with the single complaint of failing vision. He was found to have a bitemporal hemianopsia with primary optic atrophy and loss of reading vision with a greatly expanded sella turcica.

On December 19th the usual right transfrontal osteoplastic exploration was made. A large chromophile adenoma was exposed and radically excavated by a combination of electro-surgical methods and suction, restoration of the temporal fields of vision being demonstrable at the conclusion of operation. He made a perfect recovery from this procedure with no polyuria or other evidence of tuberal contusion.

Apart from the prompt restoration in vision, the only postoperative change detected was a considerable drop (20 points) in the basal metabolic rate, together with the customary loss in weight shown by acromegalics after one of these operations. He was a coöperative and intelligent young man and before his discharge willingly submitted to the tests which we proposed to make.

8.30 A.M. January 8, 1931. *Preliminary Observations.*—Fasting. Basal metabolic rate -13. Weight 85.8 kgm. Erythrocytes 5,160,000. Blood sugar 0.099. Voided 440 c. cm. urine. Rectal temperature 99.8°F.* Pulse 80. Room temperature 73°F. Respiration 21. Blood-pressure 130/80. Skin dry. Hands and feet rather cool and moist. Pupillary measurements registered.

10.39 A.M.—Injection into lateral ventricle of 1 c. cm. of "surgical pituitrin."

10.45.—Sensation of warmth. Definite flushing of skin except over site of bone flap. Sudden profuse sweating.

10.51.—Slight fall in blood-pressure. Profuse perspiration with no appreciable lachrymation, salivation or change in pulse. Complaint of intestinal uneasiness. Borborygmi auscultable. Hands and feet have become warm.

10.58.—Flushing has become very pronounced. Sweat excessive. Pillow and sheets wringing wet (cf. frontispiece).

11.00.—Temperature beginning to fall. Erythrocytes 4,550,000. Blood sugar 0.121. No pupillary change.

11.11.—Rectal temperature 99.3°. Flush persists. Slight temporary increase in pulse rate to 100. Brief preliminary drop in systolic blood-pressure to 110 now followed by pressor response to 140.

* In all these observations the continuous record of the rectal temperature has been taken on a Leeds & Northrup Resistance Thermometer Recorder.

11.20.—Temperature falling rapidly. Now 98.5°. Flush persists. Perspiration still excessive. Nauseated but no cramps.

11.30.—Rectal temperature 97.7°. Condition otherwise unchanged.

11.38.—Gradual slowing of pulse to 60 and of respiration to 12. Blood-pressure fallen to pre-injection level of 130. Rectal temperature 96.8°.

11.50.—Rectal temperature 96°. Flush fading. Perspiration much diminished.

12.00 Noon.—Rectal temperature 95.3°. Flush barely perceptible. Skin drying. Still nauseated.

12.10 P.M.—Rectal temperature 94.8°. Pulse 60.

12.20.—Rectal temperature 94.2°. Vomited 75 c. cm. of bile-stained mucous fluid.

12.30.—Rectal temperature continues at 94.2°, its lowest point, a drop of 5.6° F. in 1 hour 40 minutes. Erythrocytes 4,800,000. Blood sugar 0.114.

12.41.—Basal metabolic rate -31. Rectal temperature has started to rise, 94.4°. Beginning to feel cold though he has been well covered and room temperature at this time is 77°F.

2.30.—Weight 83.9 kgm. Loss of 1.9 kgm.

2.45.—Vomiting again, 150 c. cm. of yellow mucous fluid. Unable to void voluntarily. Bladder feels empty.

3.00 *et seq.*—Returned to ward. Rectal temperature (taken by thermometer) did not regain pre-injection level until 6 P.M. and continued to rise to a maximum of 101°F. at 2 A.M. Voided 400 c. cm. at 6 A.M. Morning rectal temperature 99.8°F. 8.30 A.M. basal metabolic rate -1, a rise of 30 points from low injection level of day before.

To summarize: The injection in this case gave a marked reaction, its more striking features being the vaso-dilatation and sweating (sparing the skin over the bone flap); the drop of 5.6°F. in body temperature in the course of an hour and a half with coincidental lowering of the basal metabolic rate from -13 to -31. Vomiting was less pronounced and more tardy in appearance than usual but the patient stated that he never vomits easily. The customary salivation and lachrymation were not noted. There was no temporary increase in erythrocytes as has been observed in some other tests though the loss of fluid from sweating would have led one to expect there might be, regardless of any effect in contraction of the spleen.

Similar injections with variable amounts of the extract (one cubic centimeter of surgical pituitrin being the customary dose) have been made up to the present time on 38 occasions in 24 subjects. The majority of the patients who have submitted to the tests were convalescing from operations for pituitary adenoma of one sort or another, the larger number of them with adenomas of chromophobe variety associated with moderate signs of pituitary insufficiency (hypopituitarism). As this clinical state is usually accompanied by more or less pallor and by an extreme dryness of the skin, the flushing and sudorific response have been the more striking. Because the operations on these patients had been conducted for the purpose of restoring vision due to pressure against the chiasm of a large adenoma, this fact implies that the posterior lobe was in all probability thrown out of function by the expanding intrasellar lesion, which might

conceivably have had some bearing on the intensity of the reaction. However, other persons without pituitary adenomas and with normal third ventricles prove to be equally susceptible to the effects of the injection.

As might be expected, due partly to individual idiosyncrasy of the subjects of these tests as well as to the variety of intracranial disorders by which they were victimized, and due partly to possible differences in the activity of the commercial preparation employed, precise standardization of which is difficult, considerable variability in the intensity of the responses has been observed from case to case. In one patient a cubic centimeter of "obstetrical pituitrin" gave no reaction whatsoever. In another, the customary cubic centimeter of "surgical pituitrin" gave only the slightest reaction; but two days later 1.5 c. cm. gave a severe reaction with the usual pronounced flush, sweating, vomiting, salivation and lachrymation with fall in temperature of 5.9°F. within two hours. In this particular instance, shivering accompanied the fall in body temperature and, contrary to the usual rule, there was a rise in the metabolic rate. Ordinarily the rate falls, a drop from -27 per cent to -50 per cent having been observed in one patient with a chromophobe adenoma.

No characteristic pupillary reaction has been detected in any case. Observations on blood sugar, on blood fat, on the erythrocyte count, have not been as yet sufficiently numerous or sufficiently striking to justify an attempt to interpret them. The expected haemodynamic response has in most cases been surprisingly slight and brief or altogether absent even when the reaction has been otherwise marked; when it has occurred there has usually been a slight slowing of the pulse. There has almost always been a temporary oliguria but the effect on the excretion of urine has been obscured by the fact that the tests have been made on fasting patients with considerable loss of fluid from vomiting and sweating.

The injection in all cases has been made into the lateral ventricle and the question naturally arises as to the way in which the extract acts when thus introduced. Two possibilities suggest themselves: (1) Resorption into the blood stream; and (2) the direct stimulation of hypothalamic nuclei by diffusion of the substance through the ependymal lining of the third ventricle. The former is highly improbable not only because of the promptitude of the reaction but for the reason already mentioned, that pituitrin when injected into the blood stream or intramuscularly has a vaso constrictor effect and causes cutaneous pallor whereas vaso-dilatation with flushing and hyperhidrosis are evoked by its intraventricular injection. Other evidence of a more negative character, which will be reserved for a subsequent paper, speaks in favor of the view that the extract must act as a direct stimulant to subependymal hypothalamic nuclei.

In three patients who have previously shown a marked reaction to

one cubic centimeter of pituitrin in the ventricle, the commercial products of "pitressin" and "pitocin" have subsequently been given in like (1 c. cm.) amounts. A slight reaction to each substance was observed in one instance but nothing comparable to the effect of pituitrin itself. In one patient, indeed, a cubic centimeter of each substance was given coincidentally with no observable effect whatsoever.

Summary.—Though extracts of the neurohypophysis are known to possess pharmacological activity, extirpation of this portion of the gland or its destruction by disease leads to no symptoms that are as yet clinically recognizable. Nevertheless histological evidence has been provided which shows: that the lobe is under control of an abundant non-myelinated nerve supply from the tuber; that the hyaline bodies of Herring probably represent the secretory product; that these bodies not only may pass into the recently discovered sinusoids of the tuber but also into the ventricular cavity. A substance having the properties of posterior lobe extract has been found by many in the cerebrospinal fluid; stimulation of the tuber has been shown to increase its amount; and commercial pituitrin injected into the ventricle has a pronounced stimulatory effect, essentially parasympathetic in character, apparently nuclear in origin, and presumably due to diffusion of the substance through the ependymal lining of the ventricle.

Conclusion.—Though the function of the neurohypophysis has been wholly overshadowed experimentally and clinically by the recent attention drawn on the one hand to the hormones of the anterior lobe and on the other to the centers in the hypothalamus, the striking response to the injection of its active principle into the ventricle not only gives additional evidence in favor of its normal passage into these cavities, but shows that the posterior lobe must play a far more important rôle in neurophysiology than has been heretofore appreciated.

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⁴ Pines, I.-L., "Über die Innervation der Hypophysis cerebri," *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1925, 100, 123-138.

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⁹ Espino, A. V., "Contribucion al estudio de las relaciones entre la hipofisis y los centros diencefálicos," *Thèse de la Faculté de Med.*, Mexico, 1924.

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¹¹ —, *La Neurocrinie Hypophysaire*, Paris, G. Doin et Cie., 1928, 102 pp.

¹² —, "La voie céphalo-rachidienne d'excretion de la colloïde hypophysaire chez le chat," *Arch. d'Anat. microscop.*, 1929, 25, 69-74.

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¹⁶ Trendelenburg, P., "Die Sekretion des Hypophysenhinterlappens in die Cerebro-spinalflüssigkeit," *Klin. Wochschr.*, 1924, 3¹, 777-779. Also: "Weitere Versuche über den Gehalt des Liquor cerebrospinalis an wirksamen Substanzen des Hypophysenhinterlappens," *Arch. expil. Path. Pharmacol.*, 1926, 114, 255-261.

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II. THE SIMILARITY IN THE RESPONSE TO POSTERIOR LOBE EXTRACT (PITUITRIN) AND TO PILOCARPINE WHEN INJECTED INTO THE CEREBRAL VENTRICLES

BY HARVEY CUSHING

Communicated March 16, 1931

In the preceding paper it was pointed out that the intraventricular injection of "pituitrin" has a profoundly different effect from that which follows its subcutaneous or intravenous administration. Instead of the customary pallor of the skin with evacuation of the bowels, there usually occurs a prompt cutaneous vaso-dilatation with an extreme sudorific effect, often with repeated vomiting and a considerable fall in body temperature.

This peculiar and striking response to pituitrin when put in the ventricles was so suggestive of the known pharmacological reaction to pilocarpine that it seemed advisable to make comparative studies of the effect of the extract and of this drug. Accordingly, in one of the patients who had shown at an earlier session a well-marked reaction to intraventricular pituitrin a test was first made with a subcutaneous injection of 12 mgm. of pilocarpine. This led to the familiar response characterized by moderate flushing, slight sweating with salivation and lachrymation, some intra-abdominal uneasiness but no vomiting, a temporary increase of 20 points in the pulse rate but no change in blood-pressure or pupils, and an insignificant fall in rectal temperature of 0.8°F. A slight rise of 7 points in the basal metabolic rate was observed but this was considered to lie within the margin of error.

On the following day, less than half of this dose of pilocarpine, namely, 5 mgm., was introduced into the lateral ventricle. Almost immediately there was a rise in pulse rate of 20 points without appreciable alteration in blood-pressure or change in size of the pupils. In a few moments the patient had a sensation of warmth soon followed by a marked generalized flush, a drenching perspiration and excessive salivation accompanied by prolonged retching and vomiting. In the course of the next two hours the temperature dropped off two degrees, from 98.8° to 96.8° but with no change in the basal metabolic rate.

This reaction was more severe than had been anticipated and in the six other patients, on whom similar tests have subsequently been made, one-half of this amount of pilocarpine, namely, 2.5 mgm., has been introduced; but this smaller dose has elicited the same prompt and striking reactions in all instances but one. The exception was in a patient who had a glioma involving the tuber and in whom the intraventricular injection of one cubic centimeter of surgical pituitrin had likewise caused no appreciable effect.

To show how nearly comparable are the reactions to the two substances administered in this way the following protocols may be given side by side.

The patient, John S., was convalescing from an operation for the removal of a large glioma of the left temporo-occipital region unassociated with hydrocephalus. At the time the tests were made his wound was healed, there was no tension and he was wholly free from symptoms. A previous intraventricular injection of 1 c. cm. of surgical pituitrin in the ventricle had caused a definite though inconspicuous response leading to a fall of temperature of one degree only and, contrary to the usual rule, a rise in metabolism from +1 to +8. He was then given a test with 2.5 mgm. of pilocarpine which evoked such a marked reaction that on a subsequent occasion, for better comparison of the two effects, a dose of 1.5 c. cm. of pituitrin was injected. The protocols of these two injections are subjoined.

REACTION TO PILOCARPINE (CF. CHART I)	REACTION TO PITUITRIN (CF. CHART II)
<i>Jan. 17, 1931. Preliminaries, 9 A.M. et seq. Basal metabolic rate -1; weight 65.4 kgm. Blood: erythrocytes 5,010,000; sugar 0.124 mgm.; total lipoids 0.652. Pupils 5 mm. (unaffected throughout). Rectal temp. 99°F.; pulse 65; blood-pressure 124/75.</i>	<i>Jan. 22, 1931. Preliminaries, 9 A.M. et seq. Basal metabolic rate, +3; weight 66.4 kgm. Blood: erythrocytes 4,290,000; sugar 0.098 mgm.; total lipoids 0.635. Pupils 4.5 mm. (unchanged throughout). Rectal temp. 98.9°F.; pulse 65; blood-pressure 124/76.</i>
10:30 Ventricular tap; 5 c. cm. fluid withdrawn.	10:28 Ventricular tap; 5 c. cm. fluid collected.
10:38 <i>Injection 2.5 mgm. pilocarpine with prompt slight enduring rise in blood-pressure to 156/95.</i>	10:38 <i>Injection 1.5 c. cm. surgical pituitrin with prompt slight enduring rise in blood-pressure to 150/90.</i>
10:43 Borborygmi; nausea; vomiting; slight flush.	10:42 Nausea; slight flush; feels warm; skin moist.
10:48 Continued vomiting; marked flush; free sweat.	10:47 Perspiring freely; salivation; lachrymation; blood for erythrocytes 4,570,000.
11:09 Periodical retching and vomiting continuous. Heavy sweat.	11:00 Marked flush; heavy sweat; nausea continues.
11:10 Temp. begins to drop (32 minutes).	11:04 Temp. begins to drop (26 minutes).
11:17 Retching; vomitus blood-streaked.	11:31 Continued rapid fall in temp. to 96.4°; no vomiting.
11:20 Blood: erythrocytes 4,950,000; sugar 0.160; total lipoids 0.685.	11:47 Blood: erythrocytes 4,450,000; sugar 0.111; total lipoids 0.657.
11:30 Sweat still profuse; retching less frequent.	12:10 Flush fading; cessation of sweat; temp. 93.8°.

REACTION TO PILOCARPINE (CF. CHART I)

(Continued)

- 12:20 Flush fading; skin drying; temp. 96.6°.
- 12:35 Reaction practically over. Temperature at lowest level, 96.4°.
- 1:00 Metabolism taken, +6. Weight 63.8 kgm.
- 1:20 Chart discontinued. Temp. at 97.2°. Blood-pressure remains slightly elevated. Rectal temperature subsequently taken half-hourly by thermometer; pre-injection temperature not regained until 3:30.

REACTION TO PITUITRIN (CF. CHART II)

(Continued)

- 12:29 Reaction about over. Temp. at lowest level, 93°. Shivering though body and extremities warm to touch.
- 1:00 Metabolism +46 (shivering); weight 64.3 kgm.
- 1:20 Metabolism +23. Temp. 94°. Comfortable; no shivering.
- 2:20 Blood; total lipoids 0.686; metabolism +22; temp. 95°.
- 3:20 Metabolism +26. Temp. 97°.
- 4:20 Metabolism +29. Temp. 97.8°. Weight 64.3 kgm. Chart discontinued. Subsequent rectal temperatures taken with thermometer half-hourly. Pre-injection temp. of 99° not regained until 7 P.M.

The *similarities* in the reactions to the given doses of pilocarpine and pituitrin noted in these protocols are possibly still more apparent from the plotted records which are here appended (Charts I and II). These charts show the prompt slight pressor response which endured throughout the period of reaction; the secondary slight slowing of pulse rate; and the downward chute in rectal temperature which began after the lapse of about half an hour. Both substances produced the same pronounced flush and drenching sweat which lasted approximately one hour and a half. There was no appreciable change in the size of the pupils with either injection.

The chief *differences* in the responses lay: (1) in the more marked vagal effect from pilocarpine with continued retching and vomiting until positive blood was shown by the guiac test whereas there was only a brief period of nausea with pituitrin; (2) in the far more pronounced and enduring fall in body temperature from pituitrin which persisted long after the cessation of the sweat, the normal rectal temperature not having been regained after the 2.6° drop due to pilocarpine until three hours had elapsed, and after the pituitrin test, with a 5.9° drop to its lowest level of 93°, not until the lapse of six and one-half hours.

One peculiarity in the reactions shown by this patient was the unexpected increase of 43 per cent in the basal metabolic rate which coincided with the lowest temperature caused by the pituitrin injection. For this astonishing reaction with the body temperature at 93° there is

no ready explanation unless it was that the patient was shivering. The finding was so contrary to the usual rule, it was repeated hourly for the next four hours, the rate as recorded in the protocol still remaining high though shivering had ceased; and on the following morning it was found to be still elevated at +13 though the patient was comfortable, composed and without fever.

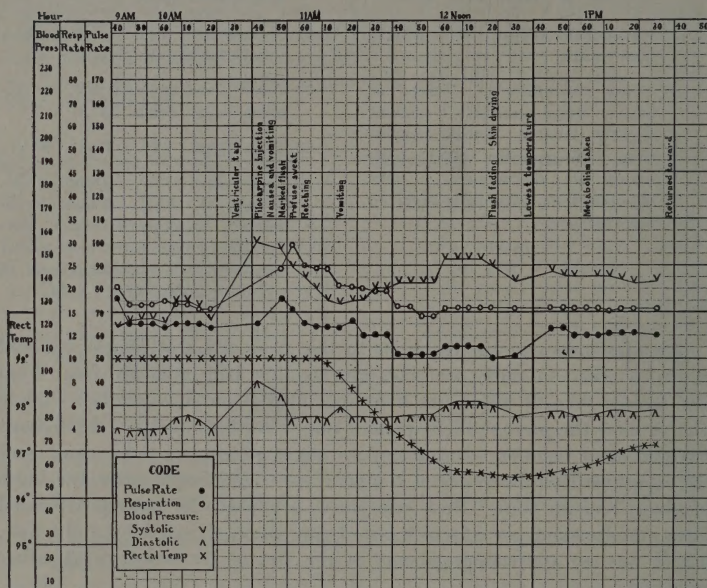


CHART I

Showing the effect on pulse rate, respiration, blood-pressure and rectal temperature of an intraventricular injection of 2.5 milligrams of pilocarpine.

At an earlier session, as mentioned above, a cubic centimeter of pituitrin had given only a mild reaction, and it may be presumed, had we cared to subject this willing man to further tests, that a dose of pilocarpine larger than 2.5 mgm. would have given as striking an antipyretic response as the 1.5 cubic centimeter dose of pituitrin evoked. In the two patients in the series who had received 5-mgm. intraventricular doses of pilocarpine, one showed a fall of 2° in temperature in one and one-half hours and the other a fall of 4.5°. Personal idiosyncrasy doubtless is but one of many factors in the variability of the reactions; the remarkable thing

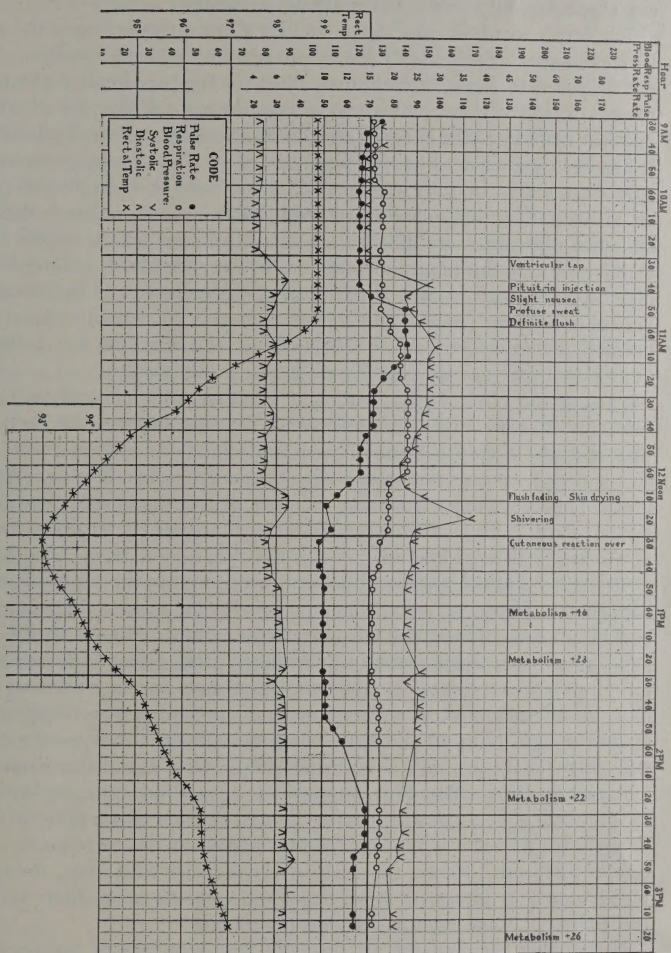


CHART II

Showing (for comparison with Chart I) the effect of 1.5 cubic centimeters of pituitrin injected into the ventricle of the same patient at a subsequent session.

is that the responses to the two substances, under the inexact circumstances of these observations, not only bear such a close resemblance but are chronologically and quantitatively so similar.

Just how and where pilocarpine and its allied drugs act upon the secretory glands seems to be not fully agreed upon by pharmacologists. They are supposed to have an excitatory effect on the peripheral nerve terminations in the various glands and at the myoneural junction of smooth muscle. And since the effect of atropine is antidotal to that of pilocarpine, it has been assumed to have a paralytic effect on the same terminal apparatus whether in salivary, gastric, pancreatic or sudoriferous glands or unstriated muscle. Some authors, indeed, have claimed that the action of muscarine and allied drugs is a direct one on the organs themselves and that the nerves are not in any way involved. However this may be, all authorities agree that the effect of these drugs on the circulation varies in different species, and so far as man is concerned neither has a haemodynamic response been observed nor any effect on the pulse rate in any dose that one would feel justified in administering.

Though the physiological action of pilocarpine is evidently expended somehow in stimulating the autonomic nervous system, the possibility that it might act on a higher center controlling the system rather than on the periphery does not seem to have been given due, if any, consideration. This may, indeed, be true of other drugs, the effects of which are similarly apt to be studied on anaesthetized animals or on pithed animals under artificial respiration.

Though the subject, whose tests have been cited in the protocols above, happened to be convalescent from an operation for a cerebral glioma which had been exposed from the side, the larger number of tests in the series have been made upon patients following frontal osteoplastic operations for pituitary adenomas. In the process of making the customary bone flap for all such procedures four or more preliminary perforations are made through the skull and these small holes make subsequent access to the ventricle by a needle even more simple than the performance of a lumbar puncture. The flap, moreover, is so outlined that its lower leg, for purposes of concealment, passes through the line of the eyebrow which necessitates division of the supraorbital nerves to the corresponding side of the forehead. Hence the scalp overlying the bone flap, though its blood supply is intact, is denervated and remains anaesthetic until, in the course of some months, the nerves reunite.

It has long been known to clinicians that paralysis of the peripheral nerves renders the corresponding skin field irresponsive to the sudorific effects of pilocarpine. This fact, utilized long ago by Victor Horsley to determine the upper level of a spinal cord lesion, has been more recently employed by Otfried Foerster as a means of mapping out the dermatomes

after the surgical division of the spinal nerve roots. However, owing to overlap of the skin fields supplied by the spinal segments, the boundary of the affected area under these circumstances is less sharply demarcated than in the operations under consideration.

As shown in Miss Codding's color sketch (frontispiece), the perfectly healed flap remains pale and dry in striking contrast to the rest of the face and body which may be greatly flushed and dripping with sweat. With a sufficient dose, either of extract or drug, to give a marked reaction the contrasting color effect in the forehead is brought out by either interventricular pilocarpine or pituitrin and also by an intramuscular injection of pilocarpine. On the other hand, the intramuscular or intravenous injection of pituitrin, as already pointed out, causes a generalized pallor which affects the skin of both sides of the forehead alike. Since the circulation of the bone flap remains intact, this would appear to indicate that the effects both of pituitrin and pilocarpine introduced by way of the ventricle are not exerted on the sweat glands through the medium of the circulating blood or of sympathetic fibres which accompany arterial blood-vessels but must be produced by effector impulses which travel from some higher center by way of the peripheral nerves, presumably along certain sensory fibres, which, in their antidromic function, behave as part of the parasympathetic system.

Both of these substances, moreover, the drug as well as the extract, give reactions that suggest a parasympathetic (bulbar) rather than a sympathetic (thoraco-lumbar) stimulation; and whether it is justifiable to assume that these supposedly reciprocal systems, if they are actually separable, are each under the control of its own higher hypothalamic center further studies may possibly show. Unquestionably the action of other drugs, particularly those of the muscarine series, when introduced into the cerebral cavities is a matter that needs ventilation.

Conclusions.—Pilocarpine and pituitrin have a similar action in producing widespread vaso-dilatation, sweating, vomiting and lowering of the body temperature when injected into the cerebral ventricles. The effects suggest a central autonomic stimulation predominantly of the parasympathetic division.

III. THE ACTION OF ATROPINE IN COUNTERACTING THE EFFECTS OF PITUITRIN AND OF PILOCARPINE INJECTED INTO THE CEREBRAL VENTRICLES

BY HARVEY CUSHING

Communicated March 16, 1931

In the two preceding papers it has been shown: (1) that the intraventricular injection of pituitrin leads to a striking response characterized by nausea and vomiting, flushing, sweating, salivation and a marked fall in body temperature usually though not always accompanied by a drop in the basal metabolic rate; and (2) that a reaction of surprisingly similar type promptly follows the intraventricular injection of pilocarpine.

Since we have in atropine an effective antidote to pilocarpine, it was felt that should the reaction of pilocarpine by way of the ventricle be checked by atropine, we might expect the pituitrin reaction to be similarly checked if the two substances, the drug and the extract, in the production of their similar effects, actually operated through the same and probably central nervous mechanism.

On one or two occasions when the reaction to pituitrin had been more marked than expected and the subject was rendered unduly uncomfortable from the recurrent retching and vomiting, it had been observed that an injection of 1 mgm. of atropine and 5 mgm. of morphia effectually checked the reaction. Under this suggestive lead, the matter was first put to test as follows:

A patient, convalescent from a highly successful operation for a chromophobe adenoma, had shown on October 14, 1930, a typical, moderately severe response to the intraventricular injection of 1 c. cm. of pituitrin with sweating, vomiting and a fall of temperature of two degrees in two hours accompanied by a drop in the basal metabolic rate from -11 to -18 . On repeating the test four days later, with the coincidental subcutaneous injection of 1 mgm. of atropine, there was no discernible response.

Another patient, likewise convalescent from a similar operation for the same malady, had shown on October 16, 1930, a somewhat tardy (30 minutes) but typical response to 1 c. cm. of pituitrin intraventricularly with moderate sweating, flushing and vomiting over a period of two hours and a drop in temperature of 1.2°F . Eight days later, 5 mgm. of intraventricular pilocarpine provoked a prompt and vigorous reaction with vomiting, sweating, flushing, lachrymation and salivation, and a drop in rectal temperature of 4.4° in 90 minutes, the basal metabolic rate remaining unchanged. After an interval of three days, on October 27, 1930, the intraventricular injection of 1 c. cm. of surgical pituitrin, when repeated with the coincidental subcutaneous injection of 1 mgm. of atropine, caused no appreciable reaction apart from a subjective dryness of the mouth, a possible slight temporary contraction of the pupils, a trifling increase in pulse rate and a moderate pressor response.

It remained to be seen whether atropine would have an inhibitory effect on the response to pituitrin as well as to pilocarpine when coinci-

dentally injected into the ventricle. A favorable opportunity to make the test occurred in the following case:

The patient, a woman 56 years of age, had been operated upon November 10, 1930, for a fairly well encapsulated left parasagittal glioma which was easily removed, apparently intact. From this operation she made an excellent recovery with perfect wound healing and no febrile reaction at any time until the 17th postoperative day when for the first time, following a series of x-ray treatments, she showed a slight wave of pyrexia reaching 102°F.

Having already come to realize the possibility that the temperature-lowering effect of intraventricular pituitrin might be utilized to combat the neurogenic hyperthermias which sometimes occur after serious operations for tumours,* though there was no reason for suspecting that this patient's mild fever was of this type, it at least gave an opportunity of seeing what would be the effect of the injection as an antipyretic.

Accordingly on November 28th at 4.25 P.M., the rectal temperature being 102.4°F., 1 c. cm. of surgical pituitrin was introduced into the ventricle with the usual, though in this instance only a moderately striking reaction, which was somewhat delayed in onset and occurred without appreciable change in pulse rate or blood-pressure. After an interval of 10 minutes there was nausea, lachrymation and salivation; in 15 minutes, the temperature had begun to drop (101.7°); in 35 minutes sweating and flushing were first definitely noted; after 60 minutes there was a copious evacuation of the bowels (temp. 100.8°); in 1 hour 20 minutes there was an initial attack of vomiting followed by other similar attacks during the course of the next two hours by which time the reaction was over, though the rectal temperature continued to fall until 8 P.M. when it was at its lowest point of 98.4°F., a drop of 4 degrees.

Four days later, December 2, 1930, with the rectal temperature at 99.8°, she was given at 9.40 A.M. an intraventricular pilocarpine test (2.5 mgm.) which gave a typical reaction as follows: There was a prompt pressor response from 110/70 to 140/80 which endured throughout the test; at the end of 5 minutes she experienced abdominal uneasiness followed by nausea and retching; after 9 minutes, first appearance of sweating, flushing and salivation soon becoming excessive; 11 minutes, an explosive, copious bowel movement;** 16 minutes, owing to patient's agitation the reaction was checked by a hypodermic injection of morphia 5 mgm. and atropine 0.5 mgm. This injection promptly quieted her and within 5 minutes, though the flush continued, the sweat had ceased together with the salivation, leaving her with a dry mouth. Periodical vomiting nevertheless recurred during the next hour and a half, the last specimen showing a positive guiac test for blood. The rectal temperature slowly dropped in the course of two hours from its initial 99.6° to 97.1°, its lowest level.

This patient, therefore, having shown a moderate reaction to an intraventricular injection of 1 c. cm. of surgical pituitrin and an unduly exaggerated one to the intraventricular injection of 2.5 mgm. of pilocarpine, permitted us to try the effect of the preliminary intraventricular injection of atropine on these responses. Accordingly, on December 4, 1930, 0.5 mgm. of atropine was introduced in the ventricle without any appreciable

* These hyperthermias are more commonly observed in children after the radical removal of median cerebellar tumours which lead to the abrupt collapse of the secondary hydrocephalic distention of the ventricle.

** It will be observed that both intraventricular pituitrin and pilocarpine in this case had an unusually definite effect on the sacral autonomic.

effect other than the sensation of dryness of the mouth and questionable slight increase in the diameter of the pupils. Thirty minutes later, one c. cm. of surgical pituitrin was introduced without any subsequent subjective effect or objective reaction whatever on the part of cardiovascular, gastrointestinal or thermo-regulatory mechanisms.*

On December 8th at 11.25 A.M., again after the usual preliminaries, another 0.5 mgm. of atropine was injected into the ventricle, the same subjective sensation as before of dryness in the mouth being produced, but there was no determinable pupillary change. Thirty minutes later 2.5 mgm. of pilocarpine was introduced, and though the tongue appeared to become somewhat more moist there was, apart from this, no observable effect of the drug whatsoever.

Whereas, after the typical response to pituitrin or pilocarpine given alone, this patient, as has been true of other subjects similarly tested, showed for some hours inappetence due to subdiaphragmatic uneasiness with waves of nausea, on the conclusion of each of the tests which were counteracted by atropine she eagerly ate a hearty lunch.

Atropine, in the opinion of pharmacologists, exercises a paralytic effect, like curare, at the peripheral nerve termination of the glands as well as at the myoneural junction of involuntary muscle. In other words, the drug supposedly acts at the same peripheral points at which pilocarpine causes its excitatory effects, the two drugs being peculiarly antidotal. These observations herein reported if correctly interpreted would seem to suggest that both drugs may act centrally as well, and if this is so they must probably operate through some diencephalic center where parasympathetic impulses may be discharged or inhibited.

Conclusion.—Atropine whether given subcutaneously or previously introduced in the cerebral ventricles appears completely to counteract the customary effect both of pilocarpine and of pituitrin when administered by way of the ventricles.

* Whether the atropine served to check the usual oliguric effect of the extract unfortunately could not be determined.

IV. THE METHOD OF ACTION OF PITUITRIN INTRODUCED INTO THE VENTRICLE

BY HARVEY CUSHING

Communicated April 14, 1931

It has been heretofore shown: (1) That the extract of the neurohypophysis (pituitrin) when injected into the cerebral ventricles usually provokes a striking and characteristic reaction; (2) that pilocarpine likewise introduced causes a highly similar response; and (3) that the preliminary administration of atropine, whether given subcutaneously or put into the ventricle, appears completely to inhibit the intraventricular response not only to the extract but to the drug.

Do these substances so introduced act peripherally after resorption into the blood-stream, or do they act directly upon subependymal and diencephalic nerve centers? In the attempt to answer this question it might be assumed, since the substances have always been injected into the lateral ventricle, that they might easily become resorbed into the blood-stream either through the ependyma or by way of the choroid plexuses which lie exposed in the ventricles.

It has been pointed out that this action by resorption is scarcely probable, at least in the case of pituitrin, because when given intramuscularly or injected into the blood-stream its effect is wholly different from that which follows its introduction into the ventricle. In the case of pilocarpine, on the other hand, no such differences in action are apparent, and it might well enough be assumed, since pilocarpine acts quickly by whatever method it is administered, that it is resorbed in some way into the blood-stream and then acts, as pharmacologists assume that it typically acts, on the myoneural junction in the case of smooth muscle and on the peripheral nerve mechanisms in the case of the secretory glands which are affected by it.

In looking for an answer to this query, as propounded, it has been felt that the several patients in whom the intraventricular injections either of pilocarpine or pituitrin have been without effect might give valuable information. The negative responses which have occasionally been observed are divisible in three principal groups: they occur (1) when an insufficient dose has been administered; (2) when the ventricles have been greatly expanded by hydrocephalus; and (3) when the interbrain has been the seat of tumour. These three groups will be separately considered.

(1) *Insufficient Dosage*.—Necessarily, owing to inexperience, the effective dose either of pituitrin or pilocarpine given in the ventricle has

been a matter of guesswork. To establish the smallest dose of any drug that will provoke a characteristic response and the largest dose that can be given with safety is a pharmacological problem difficult enough, because of individual idiosyncrasy, even in normal subjects. Nor has this been the purpose of these studies in which the tests have all been made on patients convalescent from operations for a variety of intracranial disorders. The fact that the responses which have been described occur under any circumstances is surprising enough and we must for the present let it go at that. The main point to be borne in mind is that all of the subjects (apart from those that fall in the groups 2 and 3 to follow) possess, so far as one can judge, normally reacting interbrains unaffected by the disorder for which the operations were done even in the case of the pituitary adenomas which dominate the list.

That a cubic centimeter of "surgical pituitrin" should have been hit upon as a fair average dose was purely fortuitous and even so there is great variability in the responses, from one so mild it might easily escape notice, to one so severe it is humane to check its course by a hypodermic of morphia and atropine. In one instance a cubic centimeter of the weaker "obstetrical pituitrin" failed to cause any discernible reaction whereas the same dose of surgical pituitrin gave a marked response. And in the preceding paper an experience was cited with a patient, almost certainly with a normal ventricular system, whose response to one cubic centimeter of surgical pituitrin was mild whereas the response to 1.5 c. cm. was extreme.

(2) *An Accompanying Hydrocephalus.*—On a few occasions pituitrin has been injected into hydrocephalic ventricles usually though not always with a negative effect. This might be explained in various ways: by the degree of dilution of the extract in the abundant fluid; by the possibility that secondary pathological changes of some sort in the choroid plexuses or ependyma prevent resorption; or (and what seems most probable) by the extreme distension of the third ventricle in whose paper-thin walls the nuclei, on whose stimulation the responses are assumed to depend, have either been destroyed or thrown out of function. The following experience is an example:

Mrs. P., 40 years of age, had suffered for two years from suboccipital headaches with increasingly unsteady gait and recent blurring of vision. Examination showed unmistakable signs of a cerebellar tumour with secondary hydrocephalus and a choked disc advancing to atrophy. At operation, on October 10, 1930, a large median cerebellar astrocytoma was encountered and extirpated intact together with the roof of the widely expanded fourth ventricle.

She made an excellent recovery from the operation and on October 24th an intra-ventricular injection of 1 c. cm. of surgical pituitrin was given through the burr hole which had been made over the occipital pole to tap the ventricle during the course of the operation. There was no recognizable reaction of any sort. On the following day, October 25th, 2 c.cm. of surgical pituitrin were similarly introduced again with no

determinable symptomatic response apart from a drop in urinary secretion to 400 cc. for the ensuing 24 hours.

It is assumed that in this patient the long-standing extreme dilatation of the ventricles produced by a slowly growing cerebellar tumour, which from the first must have caused some degree of hydrocephalus, had in the course of time left the hypothalamic nuclei unresponsive to the effect of the extract. Whether in such a case, now that the hydrocephalus has been relieved, the damaged hypothalamic nuclei will regain their susceptibility to the direct action of pituitrin is undetermined; but I am inclined to believe that they will.

In another instance a patient with a more acute hydrocephalus secondary to an acoustic tumour showed, after operation, a reaction to 2 c. cm. of pituitrin so marked it was checked after 45 minutes by an injection of atropine, the temperature meanwhile having dropped 2.8°F . Hence in the presence of secondary hydrocephalus a variability in the responses may be expected, depending, one may assume, on the degree of anatomical and functional alteration in the diencephalic nuclei brought about by the ventricular distension.

Still another instance may be cited. A child with a long-standing hydrocephalus of marked degree secondary to a chronic inflammatory process around the brain stem had a marked hyperthermia after the prolonged cerebellar operation undertaken to reestablish the escape of fluid. A cubic centimeter of pituitrin injected into the ventricle twice a day for several days had an apparent definite effect in lowering the temperature but there were no other appreciable symptoms.

The degree to which the walls of the third ventricle may be thinned out by a chronic hydrocephalus is well known. A typical example is shown in the accompanying photograph (Fig. 1). Histological studies of the paper-thin walls of such a ventricle show the presence of scattered nuclei but the degree of functional impairment is impossible to estimate.

(3) *With Hypothalamic Tumour Involvement.*—In this connection, though there are only two cases to report, and they were not as fully checked as one might now wish they had been, we nevertheless may feel on a little more certain ground than in the foregoing discussion regarding hydrocephalus. The essential details of the more informing of the two cases are as follows:

The patient, a married Russian Jewess, 49 years of age, was admitted to the Medical Service on September 8, 1930, with a history of vomiting and epigastric pain of two weeks' duration. There was a suspicion that she had a carcinoma of the stomach but this was finally ruled out by gastro-intestinal studies. A lumbar puncture disclosed xanthochromic fluid, and curiously enough her brother, whose cerebrospinal fluid had also been found xanthochromic, had died in the hospital several years before with the diagnosis of a cerebral tumour.

She was transferred to the Surgical Service on September 20th at which time examination showed a highly emaciated woman apparently quite unaware of her surroundings and in no seeming pain or distress, but wholly uncoöperative, incontinent, and in a peculiar speechless state of mental negativism. There was constant picking at the bedclothes, a marked clutch reflex, so that it was difficult to disengage her hands from what might be put into them, some exaggeration of the deep reflexes and an apparent stiffness of the neck. A slight, questionable papilloedema was noticed in



FIGURE 1

Showing (natural size) the extreme degree of expansion of third ventricle in obstructive hydrocephalus due to tumour of the corpora quadrigemina. Note the paper-thin walls of the ventricle above and posterior (arrows) to the chiasm (ch).

the right eye alone. There was pupillary inequality, the right usually being a little larger than the left. The neurological examination was otherwise negative. Her cranial roentgenograms showed no abnormality.

A frontal tumour, possibly metastatic, was suspected. Ventriculograms showed an irregular filling defect involving the anterior part of the third ventricle, with evidence also of a mesial filling defect in the anterior horns of both lateral ventricles, particularly the left (cf. Fig. 3).

On September 24th, a right osteoplastic flap was turned down and a subtemporal decompression made with the expectation that ventricular distension would cause a subsequent bulging of the flap which would facilitate an attack on the tumour at a later time. As a matter of fact, the decompression remained collapsed, there was no subsequent elevation of the flap or other evidence of any increase of intracranial tension up to the time of the patient's death in the hospital four weeks later.

She had been given in the interim a series of x-ray treatments, and on October 11th ventriculography was repeated to see whether the ventricles had dilated and whether there had been any advance in the filling defect caused by the lesion, but no change was demonstrable.

One peculiar thing happened on October 17th, namely, a sudden bilateral oedema of both hands associated with the rapid development of bullae (Fig. 2).

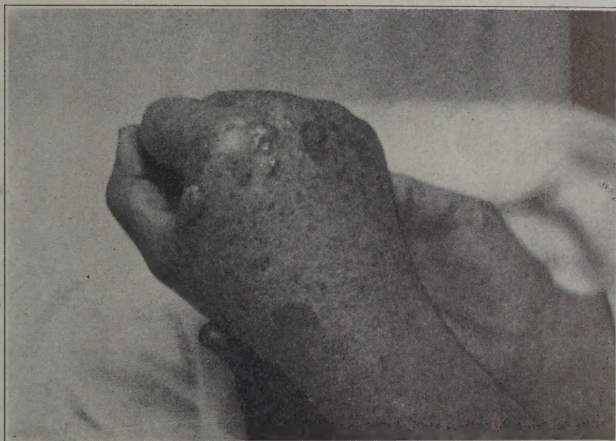


FIGURE 2

Showing the acute oedema with bullae formation in the clenched hand of the patient with tumour destroying the tuber cinereum.

Intraventricular Injections of Pituitrin and Pilocarpine.—Under the belief that the patient's symptoms of "negativism" indicated a destructive lesion of the hypothalamus it was thought justifiable to make a test with intraventricular pituitrin to see whether it would give the customary reaction. Accordingly on October 17th a cubic centimeter of surgical pituitrin was introduced with no determinable change whatsoever in rectal temperature, pulse, or blood-pressure; there was no vomiting or appreciable alteration in the color or degree of moisture of the skin.

A few days later an intraventricular injection of five milligrams of pilocarpine gave no reaction except three explosive attacks of vomiting 10 minutes, 20 minutes and 25 minutes after the injection. No other recognizable effects of the drug whatsoever were detected.

During the next three weeks there was a slow, gradual failure with progressive emaciation in spite of the fact that she took nourishment well. Though apparently conscious,

she never moved other than to hold clutched the bedclothes or whatever might have gotten into her hand; and she never spoke. She was supposed to be hypersomnolent but as she usually kept her eyes open, it was difficult to say most of the time whether she was sleeping or not. There was no evidence at any time of a polydipsia. Owing to incontinence the urine could not be measured. A sudden rise in temperature to 105° on November 17th ushered in the end.

The post-mortem examination was limited to the brain. Coronal sections showed a

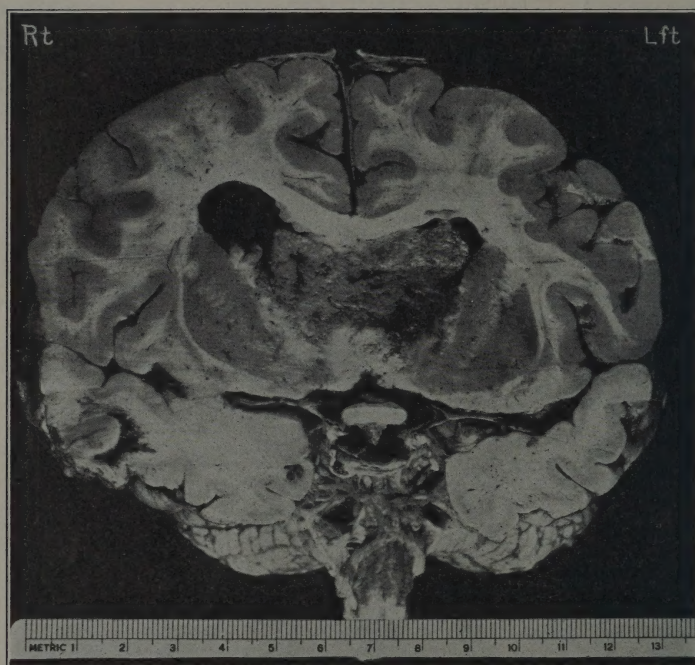


FIGURE 3

Showing the subcallosal glioma projecting into and involving the frontal horns of the ventricles. Coronal section at level of chiasm.

median, subcallosal, anteriorly placed glioma (Figs. 3 and 4). The tumour had completely destroyed the septum and had projected into the ventricles. It occupied and wiped out the anterior part of the third ventricle, leaving the foramina of Monro open and the posterior part of the third ventricle intact. There was only a slight dilatation of the lateral ventricles, within which the choroid plexuses appeared normal. A mesial section of the brain showed that a gravitation metastasis from the tumour into the infundibulum had almost completely destroyed the tuberal region (cf. Fig. 5).

This, then, was a case in which pituitrin and pilocarpine introduced into the ventricle failed to have their usual stimulatory effect, presumably owing to the neoplastic destruction of the centers concerned in the normal reaction.

A similar experience, though in the absence of a post-mortem examination somewhat less telling, was had with another Russian woman, 57 years of age, with a tumour of the third ventricle similarly demonstrated by ventriculography. She had progressive

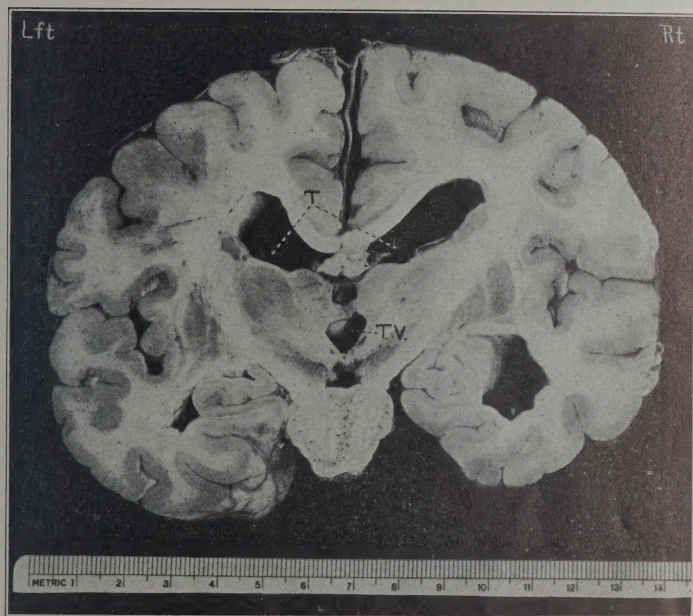


FIGURE 4

Coronal section (cf. Fig. 3) to show from behind the slight dilatation of the lateral ventricles in which tumour (T) can be faintly seen. The posterior portion of the third ventricle (T.V.) remains uninvolved.

symptoms over a period of 12 months, characterized by somnolence, mental deterioration, incontinence, and unsteadiness of gait, which were long ascribed to cerebral arteriosclerosis. In this case there was a moderate choked disc and ventriculograms showed a fairly marked expansion of the lateral ventricles, air passing freely between them, with an upward and forward displacement of the third ventricle as from a suprasellar tumour or a tumour of the ventricle itself.

In this patient also an osteoplastic flap with decompression was made, but here again

no especial evidence of pressure was found nor was there a subsequent tendency for the ventricles to fill or the flap to become elevated.

An intraventricular injection of one cubic centimeter of surgical pituitrin caused no reaction whatsoever except a slight rise in blood-pressure from 110/65 to 140/85 which persisted for the next two hours, accompanied by slight acceleration of the pulse from 65 to 75 over the same period of time. There was no change in temperature, no flushing



FIGURE 5

Mesial section of brain (natural size) for comparison with figures 3 and 4, showing the situation of the primary tumor with implantation involvement of infundibular cavity and complete destruction of tuber, (Tr) the posterior part of the third ventricle remaining free.

or sweating; a single attack of vomiting with a bowel movement occurred two hours after the injection.

It has been shown by Cannon and his co-workers¹ that an animal may survive after complete removal of its thoraco-lumbar sympathetic chain of ganglia. Similarly, it would appear that in man life may be maintained after apparent destruction of the diencephalic centers for parasympathetic action. It has been found possible on two occasions to remove extensive

tumours (ependymomas) from the third ventricle, the walls of which must have been seriously damaged in the process. Recovery in each instance nevertheless took place and the patients continue to lead essentially normal lives. It would appear, therefore, that complete paralysis of either sympathetic or parasympathetic system is less serious in its effects than abnormal or perverted stimulatory disorders affecting either system.

In contrast to these supposedly paralytic pathological conditions affecting the interbrain and which we have herein described, one may occasionally encounter irritative ones which cause stimulatory responses on the part of the autonomic system. No better example of this has appeared in the literature than that reported by Penfield² of what he calls diencephalic autonomic epilepsy. The case was that of a middle-aged woman who had a small cholesteatoma of the third ventricle which supposedly caused periodical irritation of the adjacent hypothalamus provoking peculiar seizures characterized by sudden sweating, flushing, salivation, lachrymation, hiccoughing, respiratory disturbances and fall in temperature which were regarded as evidences of autonomic stimulation. That they were essentially parasympathetic phenomena and, apart from the absence of vomiting, fully comparable to those which the intraventricular injection of a cubic centimeter of pituitrin produces is quite obvious.

Conclusions.—Negative responses to the intraventricular injection of pituitrin may occur naturally enough when the dose is insufficient and there may of course be individual variations in susceptibility to its effects. The customary responses may also fail to occur when a marked degree of hydrocephalus serves to balloon the walls of the third ventricle and also when the ventricular walls are involved by a tumour. Both of these conditions presumably serve to throw out of action the hypothalamic nuclei whose stimulation is assumed to call forth the typical reaction.

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V. THE COUNTERACTIVE EFFECT OF TRIBROMETHANOL (AVERTIN)* ON THE STIMULATORY RESPONSE TO PITUITRIN INJECTED IN THE VENTRICLE

BY HARVEY CUSHING

Communicated April 14, 1931

In the foregoing discussion of the method and place of action of pituitrin and pilocarpine when put into the ventricle, one of the arguments favoring the stimulation of hypothalamic nuclei was based on the negative responses shown by patients with pathological lesions involving the interbrain (tumour and hydrocephalus). Interpretations of physiological responses in the normal subject are difficult enough, and to bolster an argument by the absence of responses in pathological states, however suggestive they may be, is unconvincing.

Were there some certain method of experimentally inhibiting the diencephalic centers before the injections were made, their locus of action might be more definitely determined. The preliminary injection of atropine, to be sure, has been shown to be counteractive but the known antidotal effect of atropine on pilocarpine, however given, and its apparent antidotal effect on pituitrin intraventricularly administered serves possibly to exclude it from consideration. Procaine ("novocaine") immediately suggests itself but its effect as a respiratory depressant when injected into the ventricles of animals precludes its employment in man on the ground of unjustifiable risk, though the drug is employed daily for abdominal operations or even for operations on the chest and neck after its sub-arachnoid injection by the lumbar route.

To these objections of undue risk the narcotics are reasonably free though there is no unanimity among pharmacologists as to how and where hypnotics of various kinds act in the production of unconsciousness or sleep. Those who have studied the effects of cortical stimulation, whether experimentally on laboratory animals or for purposes of delimiting the motor cortex during the course of operations on the brain of man, have long known that, when the subject is under deep inhalation narcosis from ether or chloroform, cortical responses are not obtainable. Not until the twilight stage of awakening from the effects of the anaesthetic is reached does the motor cortex regain its electrical excitability.

The barbituric acid derivatives, of which several are employed for the production of surgical narcosis, are generally assumed to exercise their effect on the interbrain. Into one of these substances known as diallyl

* This commercial product is a combination of tribromethyl alcohol dissolved in amylene hydrate customarily given in a dose of one hundred milligrams per kilogram body weight.

barbituric acid ("dial-ciba"), E. and J. Keeser¹ succeeded in introducing an iron group without altering the anaesthetic property of the compound; and after it had been administered and the animal kept under its influence for several hours and then killed by bleeding, a Prussian blue reaction showed that the drug was chiefly concentrated in the thalamic and hypothalamic regions. In view of this, it is highly interesting that Fulton, Liddell and Rioch² have recently found that "dial" administered to monkeys in amounts sufficient to produce deep surgical anaesthesia leaves the electrical excitability of the cortex unimpaired, and they assume consequently that its locus of action is chiefly on sub-cortical centers, i.e., thalamus, hypothalamus, midbrain and upper medulla.

Tribromethanol (avertin), though a narcotic chemically unrelated to the barbituric acid combinations, nevertheless appears to act in precisely the same way on man that Fulton, Liddell and Rioch found "dial" to act in the ape insofar as it fails to diminish the electrical excitability of the cortex in the way that ether and chloroform do. This can be personally vouched for by the following experience:

A doctor's son had been victimized by repeated attacks of Jacksonian epilepsy invariably beginning in the right hand and occasionally passing on to unconsciousness. An osteoplastic exploration of the left hemisphere was made in the hope of finding a focal lesion that might be surgically dealt with, or, in its absence, with the intent of extirpating the pre-Rolandic hand-area. The operation was begun under local anaesthesia but the boy was so restless and uncoöperative that avertin was given per rectum, and he quickly passed into the usual profound sleep. The cortex when exposed was found hyperaemic but otherwise normal. Though the pre-central area for the upper extremity was fairly evident, to exclude any possible topographical error the cortex was stimulated by the unipolar method with a faradic current barely strong enough to cause contraction of a bundle of exposed temporal muscle. The area for the hand was thus certified, the motor responses in thumb and fingers being as sharp and easily elicited as if no anaesthetic had been used.

My personal familiarity with the barbital compounds as anaesthetics has been negligible, but tribromethanol has come to be used with sufficient frequency in the clinic so that we have a fairly definite understanding of its physiological reactions other than that producing unconsciousness. Sleep ordinarily comes on with surprising promptitude, a few minutes after the drug has been introduced into the rectum. At the same time an extreme contraction of the pupils occurs, soon followed by: (1) a definite fall in blood-pressure often as much as 30 to 50 points; (2) a slight rise in pulse in certain cases amounting to 20 to 30 beats; (3) some slight increase in respiratory rate; and (4) a slight fall in body temperature of 1 to 2 degrees. At the end of 60 to 90 minutes there is usually a fairly abrupt termination of these reactions though fluctuation in size of the pupils and in the depth of the somnolence may persist for varying lengths

of time. We have also observed a drop in blood-sugar, a considerable diminution in the erythrocyte count, and other minor changes which scarcely deserve mention as the data regarding them are insufficient.

The most striking effects of the drug are three: the *deep, apparently natural sleep*, the *pupillary contraction*, and the *fall in blood-pressure*. If these are actually central and diencephalic in origin, the hypnosis may be accounted for on the basis of stimulation of the "sleep center" assumed on experimental grounds (Hess) as well as on clinico-pathological ones (postencephalitic hypersomnia) to lie somewhere in the interbrain. It has no apparent relation to the autonomic nervous system.

Pupillary reactions, on the other hand, supposedly have such a relation and the disclosure by Karplus and Kreidl³ that electrical stimulation of the lateral wall of the hypothalamus causes dilatation of the pupils was what first led to the belief that there must be a higher "sympathetic center" in the interbrain. Just how one is to explain the prolonged fall in blood-pressure and the drop in erythrocytes unless by an expansion of the spleen is not clear, but it is at least evident that the reaction is the reverse of that which customarily follows the injection of pituitrin and pilocarpine in the ventricles. What is more, the most notable difference between the hypnotic state produced by avertin and the narcosis due to ether or chloroform is the absence of any subsequent vagal effect from the former, postanaesthetic vomiting being most unusual. This, again, runs counter to what we have found to occur after the intraventricular injection of pituitrin, the presumably vagal effect of which in the production of repeated retching and vomiting is striking. Another contrast lies in the dryness of the skin and mouth under avertin and the sweating and salivation that follow the intraventricular injection of the extract.

All things considered then, tribromethanol (should it really act on the hypothalamus when given rectally) and pituitrin (should it similarly thus act when given intraventricularly) are so definitely opposed in their effects one would expect them to be antidotal. The truth of this conjecture appears to be substantiated by the experiences cited in the following two protocols, A and B:

PROTOCOL A. (1) *A typical reaction to 1 c. cm. surgical pituitrin injected in the ventricle.* (2) *No reaction to the same injection with the patient under avertin.* (3) *A typical reaction to 2.5 mgm. pilocarpine in the ventricle.*

The patient, a man 53 years of age, was satisfactorily convalescing from an operation performed Dec. 2, 1930, for a glioma of the temporal lobe which had not served to cause hydrocephalus. At the time of the test he was wholly free from symptoms relating either to the lesion or his operation.

On December 18, 1930, after the usual preliminaries, at 10.03 A.M., 1 c. cm. of pituitrin was introduced into the ventricle with prompt moderate cutaneous flush, sweating, and salivation, but with only a slight fall in rectal temperature of less than one degree. The most striking effect, though it was unusually delayed, was the vomiting which set

in suddenly about an hour after the injection and which, accompanied by hiccoughing, continued off and on for the next three hours. It was estimated that he must have vomited 500 c. cm. of gastric secretion. This at first was clear, serous fluid but subsequently contained thick, tenacious mucous, finally became bile-stained and had a normal gastric acidity. The frothy character of the secretions suggested some hypersecretion from the lungs but no rales were heard on auscultation.

The erythrocytes, which before the pituitrin injection numbered 4,040,000, were counted 90 minutes later at 4,300,000; and at the end of 3½ hours they were 4,170,000. The temperature began to drop in 35 minutes but fell only 1.1° and the basal metabolic rate remained unaffected. Blood-sugar before and after the injection showed no essential change. There was the usual slight rise in blood-pressure from 110/60 to 130/80 which endured for three hours together with a slight increase in pulse rate instead of the customary slowing.

The vomiting had been so persistent and disturbing that at 1.40 P.M. it was checked by a hypodermic injection of 0.5 mgm. of atropine with 5 mgm. of morphia.

This patient, then, showed to intraventricular pituitrin a definite reaction in which retching and vomiting were unusually pronounced. The type of reaction therefore was eminently suitable for a test to determine whether it would be abolished or modified by avertin anaesthesia.

Accordingly, on December 23rd, after the usual preliminaries with the patient fasting, the standard dose of avertin per kilogram body weight was slowly introduced per rectum at 9.35 A.M. with an almost immediate profound sleep, a fall in blood-pressure from 130/70 to 80/60, immediate contraction of the pupils to pinpoint size, increase in pulse rate from 90 to 120, an increase in respiration from 20 to 30. These characteristic reactions were practically over at the expiration of an hour and forty minutes by which time the patient had begun to show some signs of returning consciousness.

At 11.30 A.M., two hours after the avertin administration, 1 c. cm. of pituitrin was put into the ventricle and so far as could be seen this had not the slightest effect. The skin and mucous membrane remained dry. The rectal temperature, which under avertin had dropped from 99° to 96.2°, had begun to rise at 10.50 A. M. and the curve was not affected by the injection of pituitrin forty minutes later. An insignificant fall in blood-sugar was detected when the temperature was at its lowest. The erythrocyte count remained constant within limits of error. *The excessive bouts of retching and vomiting, which had previously been produced by intraventricular pituitrin when given independently, were completely counteracted by the action of avertin.*

Three days later, on December 26th, an intraventricular injection of 2 mgm. of pilocarpine, without preceding avertin narcosis, produced a typical reaction very similar to that caused by pituitrin alone.

The counteractive effect of avertin in the second case to follow was even more striking in that 1.5 c. cm. of surgical pituitrin was injected, an amount of the extract which from a previous experience with the same patient had given an excessive reaction as related in an earlier paper in the series (No. II) in which the effects of intraventricular pilocarpine and pituitrin were contrasted.

PROTOCOL B. *A severe reaction to 1.5 c. cm. intraventricular pituitrin. Under avertin hypnosis the reaction to the same dose of the extract almost completely counteracted.*

The patient, a man 58 years of age, convalescent from an operation for the removal of a temporal glioma and at the time of the tests free from symptoms, had been found to give a typical but mild reaction to 1 c. cm. of surgical pituitrin and a severe reaction to 2.5 mgm. of pilocarpine. Consequently, the better to contrast the effect of the drug and the extract, he was then given 1.5 c. cm. of surgical pituitrin in the ventricles with the results recorded in another connection, viz., prompt flushing, sweating, salivation, lachrymation, retching and vomiting, rise in blood-pressure, slowing of pulse, and a drop of 6°F. in body temperature accompanied by an astonishing rise in metabolism of +43 per cent associated with shivering.

The effect of avertin on this patient was known from two previous experiences. The drug caused a prompt and deep hypnosis, marked pupillary contraction, a drop in the erythrocytes of 400,000, and a fall in blood-pressure from 110/70 to 70/40 with fairly abrupt return to normal on first signs of awaking at the expiration of 90 minutes.

On March 5, 1931, after the usual preliminaries, 6.9 c. cm. of avertin in 280 c.cm. of water were introduced into the rectum at 10.12 A.M. Within 10 minutes the pupils had contracted to pinpoints and he was in a profound sleep. By 10.35 the blood-pressure had fallen from 135/80 to 90/65 and the erythrocytes had dropped from 5,650,000 to 5,080,000. The rectal temperature remained level at 98°F. The skin was warm and dry. At 10.42 A.M. the ventricle was tapped and 1.5 c. cm. of surgical pituitrin was introduced. This had no apparent effect whatsoever. At 11.37 the patient began to arouse, the pupils dilated, and he asked for a drink of water.

At 11.45 he was sufficiently awake to respond to commands and the blood-pressure had begun to rise, 110/70. At this time, 93 minutes after the avertin was given and 63 minutes after the pituitrin was injected, the previously dry mucous membrane of the mouth began to show some moisture and visible beads of perspiration appeared on the skin. This mild reaction lasted for 45 minutes before it had wholly disappeared. Meanwhile the temperature dropped from 98° to 96.4°. At 12.50 when the temperature was at its lowest level, the metabolism which at the outset was zero was found to be -2, in other words, it was unchanged within the limit of error. There was no nausea or vomiting or discomfort of any kind and on returning to the ward the patient took his dinner with appetite.

In the first of these cases, therefore, avertin served completely to offset the patient's known reaction to one cubic centimeter of intraventricular pituitrin (vomiting, retching, salivation, flushing, sweating, rise in blood-pressure, etc.) when given by itself. In the second case, the larger dose of 1.5 c. cm., which had at a previous session caused a severe reaction with an unusually marked fall in temperature, gave evidence of a trifling and much delayed pituitrin effect shown by transient sweating and a slight fall in temperature after the inhibitory influence of the avertin had begun to wear away.

It can be seen that the pharmacological action on hypothalamic centers of intraventricular pituitrin and of avertin is definitely antagonistic. The chief discord lies in the pupillary contraction under the blood-borne avertin and the absence of any notable pupillary effect from pituitrin which is assumed to act by diffusion through the ependyma. This, however, may well be accounted for on the grounds that the pupillary center lies too deep to be acted upon by resorption, and it may be noted

that no pupillary dilatation was observed when atropin was injected into the ventricle. In the recent experiments of Karplus and Peczenik⁴ previously referred to, it was shown that in the cat electrical stimulation of the tuber cinereum does not cause enlargement of the pupil but that it occurs only when the outer walls of the hypothalamus itself are stimulated. Stimulation at either point nevertheless apparently serves to discharge the posterior lobe and thereby to increase the oxytocic and melanophore-expanding properties of the cerebrospinal fluid.

Conclusion.—The hypnotic tribromethanol (avertin) presumably causes its effects by action on centers in the diencephalon, and serves to counteract the stimulatory responses to pituitrin injected into the ventricles.

¹ Keeser, E. and J., "Über die Lokalisation des Veronals, der Phenyläthyl- und Diallylbarbitursäure im Gehirn," *Arch. exper. Path. Pharmac.*, 1927, **125**, 251-256.

² Fulton, J. F., and E. G. T. Liddell and D. M. Rioch, "'Dial' as a Surgical Anaesthetic for Neurological Operations, with Observations on the Nature of Its Action," *J. Pharmacol. Exper. Therap.*, 1930, **40**, 423-432.

³ Karplus, I. P., and A. Kreidl, "Gehirn und Sympathicus," *Arch. ges. Physiol.*, 1909, **129**, 138-144.; *Ibid.*, 1910, **135**, 401-406.; *Ibid.*, 1911, **143**, 109-127.

⁴ Karplus, I. P., and O. Peczenik, "Über die Beeinflussung der Hypophysentätigkeit durch die Erregung des Hypothalamus," *Arch. ges. Physiol.*, **225**, 654-669, 1930.

VI. CONCERNING A POSSIBLE "PARASYMPATHETIC CENTER" IN THE DIENCEPHALON

BY HARVEY CUSHING

Communicated April 14, 1931

In this series of papers it has been shown:

(1) That the injection of commercial pituitrin into the cerebral ventricles produces a prompt and characteristic reaction presumably stimulatory in character; (2) that pilocarpine similarly introduced gives a wholly comparable response; (3) that an antecedent subcutaneous or intraventricular injection of atropine counteracts the action both of the extract and of the drug; (4) that the effector responses do not occur in the presence of lesions which either have destroyed or which appear to have impaired the functional activity of the interbrain, more particularly its hypothalamo-tuberal portion; and (5) that with patients under the influence of tribromethanol, a narcotic which presumably acts upon diencephalic centers, intraventricular pituitrin has either no effect or one which is slight and much delayed.

While the clinical tests which have been described have been under way, efforts have been made to supplement and check them by corresponding observations in the experimental laboratory. Though there is no belittling the greater difficulty both of carrying out and of interpreting similar pharmacological tests conducted on the lower animals, some progress has nevertheless been made by my junior co-workers, Drs. Light, Lawrence, Dial, Boyes and Strayer, who will have some reports of their own to make on the subject. It may suffice at this time to say that the responses to intravenous and to intraventricular pituitrin in the dog are similar to those seen in man. The intravenous injection causes, as others have shown,¹ what appears to be chiefly a sympathetic effect, namely, an extreme pallor of skin and mucous membrane with contraction of the spleen from a vascular rather than capsular constriction. The intraventricular injection on the other hand causes a wholly different and apparently a parasympathetic reaction, namely, vascular dilatation, excessive panting, salivation, signs of pulmonary oedema and gastro-intestinal hypertonicity.

Corresponding studies on primates have been made by J. F. Fulton and his co-workers in the Physiological Laboratory at Yale; and I am permitted to state that they find the intraventricular injection of pituitrin in monkeys to have an effect corresponding in a general way to that which occurs in man, though no comparable antipyretic reactions have been observed. Much labor necessarily lies ahead before the finer details of the responses can be thoroughly worked out.

In our own experimental laboratory chief attention has been paid to the effects of the injections on splenic contracture, on blood fat, and so on, which have required repetitions of observations scarcely justifiable

on patients in the clinic, however willing they may be. Dr. Light, moreover, has shown that pilocarpine put in the ventricles of rabbits will cause gastric ulcers in a much smaller dose than Underhill and Freiheit² found necessary to produce the same effects when the drug was given subcutaneously.

In seeking to correlate and explain these observations both on man and animals, it has been assumed that pituitrin and pilocarpine are capable of stimulating hypothalamic nuclei which preside over important so-called vegetative functions. And since many of the responses like vaso-dilatation, sweating, salivation, lachrymation, and gastric hypersecretion with retching and vomiting are suggestive of a parasympathetic effect, the existence of a "parasympathetic center" in the interbrain has naturally been postulated.

For a surgeon to suggest an interpretation of matters so complicated and so far removed from his legitimate field would savour of impudence were it not that the surgery of the autonomic nervous system, though still in its infancy, has made rapid strides since the periarterial sympathectomy of Leriche and Royle's operation of ramisection came into vogue. And even should the interpretation of the effects, that have been observed to follow the intraventricular injections as described, prove to be wrong, it may, like the ardently combated views of Hunter and Royle, be provocative of new investigations of old problems, not without profit; and the neurosurgeon unquestionably will come to take part in them.

Historical Review.—The largely unmyelinated neurones composing the autonomic (Langley) or vegetative (Meyer) nervous system, all agree, play upon structures and organs that are wholly or in large part automatically controlled. Based chiefly on the discovery of the preganglionic relay of fibres to the paravertebral chain of ganglia, the involuntary nervous system has come to be divided into two structurally distinguishable divisions: namely, the sympathetic or thoraco-lumbar division which serves to separate the more headward or cranial and the more caudal or sacral divisions. These cranial and sacral divisions, which have been found to act more or less in definite opposition to the thoraco-lumbar or sympathetic division, have been variously designated, but Langley's term "parasympathetic" has come to be commonly employed for them.

Known by whatever name, these three divisions of the autonomic system, unlike the sensori-motor apparatus, which up to the time of Gaskell, Langley and Anderson had largely dominated neurophysiological research, supposedly act upon the glandular structures and smooth muscle of the blood-vessels and viscera through involuntary automatic reflex arcs. The reflex centers for the preganglionic sympathetic fibres came to be anatomically identified in the lateral horn of the gray matter of the

cord, whereas those for the cranial autonomic were experimentally located somewhere in midbrain and medulla.

But however independent of volition and the cerebral cortex these divisions of the autonomic system may be, ever since Karplus and Kreidl³ found in 1909 that electrical stimulation of the hypothalamus (*Zwischenhirnbasis*) gave a sympathetic effect in dilatating the pupils, contracting blood-vessels, and accelerating secretions, there has been a growing tendency among physiologists to accept the probability of a higher center at least for the sympathetic division of the system. The Vienna school, indeed, has been largely responsible for the promulgation of this idea to which not only Karplus and Kreidl, but Ascher and Erdheim contributed in their attribution of presupposed pituitary symptoms to lesions of the hypothalamus or tuber. The matter was soon taken up from a pharmacological standpoint by Hans Horst Meyer⁴ (1912) who with Gottlieb in the successive editions of their "Experimentelle Pharmakologie" have accepted the existence of special higher centers for parasympathetic as well as sympathetic systems, both of which are specifically acted on by drugs.

Whereas adrenalin supposedly acts on the sympathetic nerve endings in precisely the same manner as does a general sympathetic stimulation, the effect of poisons of the pilocarpine group, which are effectively counteracted by atropine, corresponds in the opinion of Meyer and Gottlieb to a parasympathetic stimulation. They, however, are obliged to admit that the striking effect of these poisons in the cutaneous glands has not as yet been proved to be wholly parasympathetic though, this exception to the general rule of opposite action of sympathetic and parasympathetic stimulation is, they believe, only an apparent one which will come to be explained by further investigation of the method of innervation.

Though the opportunity of testing the intraventricular action of drugs that influence one or another division of the autonomic nervous system has not been grasped by pharmacologists, Meyer and Gottlieb make certain statements that are highly pertinent to the subject at hand. They state for example (*loc. cit.*, IV. Auflage, page 158), that irritation of the sympathetic system increases metabolism and body temperature whereas the parasympathetic system appears—without its being possible as yet precisely to prove the matter—to lead to the opposite effect. Since a similar pharmacological reaction implies a similar chemical structure, all sympathetic end organs must be chemically alike and all parasympathetic ones equally so. And in illustration of this pharmacological law they point out that picrotoxin, for example, stimulates the parasympathetic system throughout "sometimes not only in the end organs but centrally" and that tetrahydro- β -naphthylamin similarly excites both centrally and peripherally the sympathetic (thoraco-lumbar) apparatus. Whether by

"centrally" the authors mean anything higher than the brain stem is not clear, but they may well enough have had the diencephalon in mind.

From the physiologist's point of view, no one in later years has given a more vivid account than Cannon⁵ of the manner of action of the autonomic nervous system, more particularly of its intermediary thoracolumbar division. In his more recent papers in which the general features of his many contributions have been summarized, he chooses to introduce these new terms: "exteroffective" for the voluntary sensori-motor nervous system, and "interofective" for the involuntary or autonomic system. The chief function of this latter system, through its action chiefly on smooth muscle and glands, is to preserve stability ("homeostasis") of the internal economy. Cannon particularly stresses the importance of the thoracolumbar division of this interofective system, for through its ability to mobilize the body reserves it may properly be regarded as the special and immediate agency of homeostasis. He emphasizes, too, that the principal effect of the morphological arrangement of relayed neurones in the thoraco-lumbar region is to make possible a diffuse discharge of nerve impulses which constrict blood-vessels, inhibit the activity of the digestive canal, etc., and at the same time lead to a discharge of adrenalin, the hormone and the nervous impulses working together as a sympathico-adrenal system to produce throughout the organism widespread changes in smooth muscle and glands which are largely defensive in their purport.

Now at the same time it is recognized that the cranial and sacral or parasympathetic divisions of this interofective or autonomic system work more or less in antagonism to the sympathetic (thoraco-lumbar) division. Thus, to give some familiar examples, stimulation of the sympathetic inhibits the muscular tone of the stomach, stimulation of the vagus, which is part of the cranial parasympathetic, increases it; stimulation of the sympathetic dilates the pupil, of the parasympathetic fibres in the oculomotorius contracts it, etc. But this principle of antagonism in the two systems begins to be somewhat less definite in the matter of vaso-constriction and vaso-dilatation; and when we come to the question of sweating, the rule of opposite action appears to have entirely fallen down.

Still another difference in the two systems, as emphasized by Cannon, lies in the fact that the parasympathetic fibres are anatomically so distributed as to favor more or less independent or discriminating activities in contrast to the diffuse action of the sympathico-adrenal system. This is shown in the contraction of the pupils by light, in salivation at the sight of food, in lachrymation, in gastric secretion, and so on, all of these reactions occurring normally quite independently of one another. But this, it seems to me, may merely be a question of strength of stimulus, for the effects we have observed from the injection of pituitrin into the

ventricle indicate an apparent diffuse discharge of the parasympathetic system (at least of its cranial portion) as definite as the diffuse discharge of the thoraco-lumbar system which has been the chief object of Cannon's studies.

In thus assuming that the retching and vomiting, salivation, lachrymation, vaso-dilatation and sweating, as well as the effect on the metabolism of water and of fat and also the extraordinary loss of body heat called out by intraventricular pituitrin, represent a diffuse parasympathetic discharge, the posterior lobe hormone may be looked upon as playing by central action very much the same rôle that adrenalin plays by peripheral action in prolonging and intensifying the diffuse discharge of the sympathetic division. Of the two systems, indeed, the parasympathetic, in view of its evident close relation to diencephalo-hypophysial mechanisms, would seem to be far the more important. But this would be difficult to prove, for the cranial autonomic system does not lend itself to experimental extirpation as does the thoraco-lumbar division, the complete removal of which has been so brilliantly accomplished by Cannon⁶ and his associates with the surprising disclosure that completely sympathectomized animals may survive for an indefinite time if protected from undue exposure to cold and rendered exempt from the stresses and strains which the struggle for existence would ordinarily call for.

In spite of Cannon's emphasis on the peripheral sympathico-adrenal apparatus, he at the same time has done more than any other to show how it is influenced centrally by primitive emotions; and his studies,⁷ supplemented by those of his pupil, Philip Bard,⁸ on what they call "sham rage" in decorticated animals, have served to prove the existence of an emotional center in the diencephalon which ordinarily is under some inhibitory influence by the frontal cortex. And it was subsequently shown by Fulton and Ingraham⁹ that chronic states reminiscent of "sham rage" could be produced in animals by experimental severance of the fibres that pass to the interbrain from the cortical centers.

In short, emotions such as pain, fear, rage, or a strong excitement of any kind instantly abolish the secretion of saliva, of gastric juice, of pancreatic juice, and of bile, the action apparently (if Cannon is rightly understood) occurring through central stimulation of the sympathico-adrenal (thoraco-lumbar) apparatus. But it would appear that an equally strong case might be presented in favor of the inhibition of the parasympathetic apparatus by these emotional states if a center for this apparatus in the interbrain has any basis in fact.

Since pituitrin when given subcutaneously or intravenously appears to act much like adrenalin as a vaso-constrictor, whereas its effects when put into the ventricle appear to be parasympathetic, it is not unlikely that the posterior lobe hormone may exercise a far greater influence on

the three divisions of the autonomic system than has been heretofore suspected. It is possible, too, that its cleavage products, vasopressin (pitressin) and oxytocin (pitocin) isolated by Kamm and his co-workers¹⁰ may not act in the ventricle but only peripherally; and further tests in this direction may throw light on the controversial theories of unitary *versus* multiple hormones for the posterior pituitary.¹¹

The Antipyretic, Vaso-dilator and Diaphoretic Effects.—Since the lowering of body temperature, vaso-dilatation and diaphoresis are the three most striking phenomena of the intraventricular-pituitrin reaction, they may deserve brief separate consideration.

The Antipyretic Effects.—Forty years ago, Ott¹² first briefly stated that punctures of the tuber cinereum in rabbits or cats served to stimulate what he called a "thermolytic center," and since that time the possible existence of a heat center or centers at the base of the brain has been investigated by many others who have used a variety of experimental methods. It was found by Isenschmid and Schnitzler¹³ that after bilateral removal of the forebrain, of the cerebral hemispheres, striatum and most of the thalamus, a rabbit is still capable of normal heat regulation; but this capacity, once the tuber cinereum is excluded, wholly disappears. Experimental cooling or warming of the region by altering the temperature of the arterial blood-vessels, carotid and vertebral, which supply it (Kahn) or by artificially cooling or warming the region by direct irrigation (Barbour) have been shown to have marked effects on the thermoregulatory mechanism. Hans Meyer, indeed, has postulated the existence of a "heating" as well as a "cooling" center which, though opposed in action, work hand in hand as a regulating apparatus, fever toxins for example acting on the one, antipyretics acting on the other. What is more, it is appreciated that these centers not only lie in the interbrain but send impulses through the autonomic nervous system; and Meyer goes so far as to say that the *Wärm-centrum* acts through the sympathetic and that the *Kühlcentrum* acts through the parasympathetic. Whether or not this hypothesis is actually open to proof, it at least offers an explanation of the extraordinary antipyretic effect of intraventricular pituitrin which accords with the other responses that are interpreted as being definitely parasympathetic in character.

Barbour and his co-workers have called attention to the fact that heating the carotid blood and cooling the vertebral blood have very similar effects; and they believe that they have shown thereby the existence of two functionally opposed nervous fields, the cooling center being located in the hypothalamic center, the heating center in the medullo-pontine region.

Though the "centers" which govern shivering, at least in the rabbit, have been shown by Dworkin¹⁴ to be rather diffuse, he regards them as an

integral part of the heat-regulating mechanism and believes that they are coördinated for service by a superior presiding center in the interbrain. Shivering has only been observed after one of the many tests with intraventricular injection of pituitrin or pilocarpine even when there was a marked fall in temperature, this particular reaction having occurred in a patient who showed, contrary to the usual rule, a marked increase rather than the usual decrease in basal metabolic rate. Apart from this particular case, there has been no exception to the rule that intraventricular pituitrin when it has an effect at all marked either inhibits the mechanisms involved in heat production or, what is more probable, stimulates those involved in heat loss, and these latter are regarded as predominantly parasympathetic in nature.

Stimulation of the sympathetic (thoraco-lumbar) system is known to increase body temperature and Cannon has shown that animals experimentally deprived of this apparatus are prone to lose heat on exposure to cold. What is more, when excited, sympathectomized animals have a tendency to lose heat—an antipyretic effect which might conceivably be explained on the basis of stimulation of an unopposed and still intact parasympathetic apparatus.

Vaso-dilation and Sweating.—In the subjects whose responses to intraventricular pituitrin and pilocarpine have been described, the extremities have been warm to the touch and the patients have felt subjectively warm even when their rectal temperature has been at its lowest. Conversely, patients with hyperthermia, such as occurs after certain intracranial operations, may have a rectal temperature of 106°F. even though their extremities possess a death-like coldness and clamminess to the touch. Though this, from the standpoint of sweating, sounds somewhat confusing and contradictory, it is safe to say that vaso-dilatation, sweating and the regulation of body temperature are closely related processes even though opinions concerning them, which are almost entirely built up from observations on lower animals, are highly controversial.

Vaso-constriction being admittedly the outstanding effect of sympathico-adrenal stimulation, one would assume on the principle of functional antagonism between the sympathetic and parasympathetic systems that vaso-dilatation would be the normal response to parasympathetic stimulation. But the relation of sweating to these two parts of the involuntary nervous system is highly obscure, it being generally believed by physiologists and clinicians that the sweat glands—at least those of the face and neck—can be activated by either of the opposed divisions.

The pharmacological effects of muscarine, histamine, pilocarpine physostigmine and acetylcholine when given systemically are essentially sudorific and vaso-dilator, and to these better known diaphoretic drugs intraventricular pituitrin must now be added. Though the intraventricu-

lar effect of the other substances remains to be studied, pilocarpine at least, as has been made clear, causes generalized flushing and sweating together with a more marked fall in body temperature than could well be accounted for by the effect of evaporation alone.

Sweating and vaso-dilatation, though they customarily go hand in hand, do not necessarily do so, and they have usually been studied independently of one another. Since 1876 when Ostroumoff and Luchsinger showed that faradic stimulation of the severed sciatic nerve could produce sweating in an amputated cat's leg or in one whose circulation was shut off by ligation of the abdominal aorta, the foot-pads of the cat have been the locus, favored by physiologists and pharmacologists alike, for estimating the effect of procedures and of drugs that influence sweating. From the classical paper of Max Levy¹⁵ in 1892 to the studies of Hasama¹⁶ nearly forty years later, it has been the chief method of estimating sudorific responses.

Burn's investigations,¹⁷ which were limited to a consideration of the peripheral mechanisms in animals and which carried the subject about as far as laboratory methods permit, led to the conclusions: That pilocarpine had a dilator action on the vessels; that after denervation of the leg a sweat response to pilocarpine persists only so long as vaso-dilatation persists; that the loss of the sweating and dilator response is not due to degeneration of the sympathetic or sensory nerve fibres but rather to degeneration of the motor fibres of the leg muscles; that the amount of sweat secretion produced by a central stimulus depends upon the blood-flow through the foot-pads; that the exaggeration of the sweat responses to pilocarpine after sympathetic degeneration is due mainly to removal of sympathetic control of the blood-vessels.

In contrast to Burn's laboratory observations, in which the possible active participation of the parasympathetic system in the phenomenon of sweating does not seem to have been considered, one may turn to the observations on man which have already been made and which are likely to be made in still greater number in the future now that the involuntary nervous system has come to be the object of attack by surgeons. The most informing and most detailed studies so far reported are those by Otfried Foerster and by his co-workers, Guttman and List,¹⁸ the results of which are assembled in the concluding sections of Foerster's elaborate treatise on the effect of gunshot wounds on the peripheral nerves.¹⁹

Foerster assumes the existence, for the diaphoretic mechanism, of a higher diencephalic and a lower bulbar center whence the fibres descend in the cord to emerge by way of the anterior spinal roots. He has found that stimulation of a posterior root after its division causes vaso-dilatation confined to the spinal dermatome concerned, whereas subsequent stimulation of the corresponding anterior root causes sweating and a pilomotor

response without vaso-dilatation over a much wider field, the central strip which previously showed vaso-dilatation from posterior root division remaining dry. Thus sweat fibres unquestionably leave the cord by the anterior root and active efferent vaso-dilator fibres by the posterior root, the two acting quite independently.

Foerster has further shown: That stimulation of purely sensory peripheral nerves causes both sweating and vaso-dilatation in the area of cutaneous distribution; that total division of a mixed nerve leads to significant vaso-dilatation over the area of its cutaneous distribution, and though in some cases pilocarpine may continue to cause sweating in this area, it soon loses this effect with resultant total anhidrosis; and that division of the sympathetic paths completely checks the hyperhidrosis produced by external heat, but does not in any way affect that induced by pilocarpine. In other words, sweating produced by external heat and by pilocarpine act somewhat differently. From these and other observations Foerster had been led to conclude that in the peripheral nerves there are two sets of sweat fibres, one sympathetic and the other set, which reacts to pilocarpine, parasympathetic. Where the latter have their higher centers and how the fibres run in the peripheral nerves he does not pretend to say.*

The investigations by Burn on animals and by Foerster on man which have thus been briefly reviewed have been restricted, as we have seen, to the peripheral mechanisms concerned in vaso-dilatation and sweating; and though Foerster at least predicated the existence of higher centers of control, these had not been made the particular object of a detailed study until the matter was taken up by Hasama, a Japanese pharmacologist. In his three important papers¹⁵ Hasama has shown elaborately and conclusively that mechanical, thermic, chemical and electrical methods will all serve to affect both sweating and the thermo-regulatory apparatus, whether the stimulus is applied to centers in the interbrain or to others which presumably are directly subsidiary and which lie in the floor of the fourth ventricle, more especially the dorsal nucleus of the vagus. As Hans Meyer was led to predicate the existence of separate warming and cooling centers, one sympathetic and the other parasympathetic, so Hasama has concluded from his studies that there are two kinds of centrally induced sweating, one parasympathetic associated with vaso-dilatation, and the other sympathetic or "cold" sweating.

But it is fair to say that neither mechanical, thermic, chemical or pharmacological excitation, however much information may be gained thereby, represents the natural way of affecting the diencephalic centers with which we are concerned; and reasons have been advanced whereby it may be at least assumed that the posterior lobe hormone may actually

* By electrically stimulating the surfaces of the serially transected brain and medulla

be the normal excitant, albeit the extract must be administered in a far larger dose than normally is present in order that we may unmistakably recognize its effects. And one striking feature of this vaso-dilator and diaphoretic response called forth by pituitrin is the surprising coincidental antipyretic effect, the like of which does not seem to have been observed or to occur in animals.

Conclusions.—The information in this series of papers, on which an hypothesis has been built up regarding the action of the posterior pituitary hormone on an assumed parasympathetic center in the interbrain, may be briefly summarized as follows:

(A) The active principle of the neurohypophysis is in part excreted into the blood-stream and in part into the cerebrospinal fluid. The hormone when experimentally introduced into the blood-stream causes pallor from vaso-constriction and stimulates the musculature of the lower bowel; when introduced into the ventricle, on the contrary, it causes flushing, sweating, salivation, lachrymation, vomiting and a pronounced fall in body temperature. The former bears resemblance to a sympathetic discharge combined with a sacro-autonomic effect; the latter appears to be essentially a cranial autonomic or parasympathetic effect. Pilocarpine introduced into the ventricle gives a highly similar response.

These responses to intraventricular pituitrin and pilocarpine are counteracted by atropine whether given subcutaneously or intraventricularly; they moreover appear to be abolished when the tuberal portion of the interbrain is highly distended by hydrocephalus or is the seat of tumour; and their action furthermore is checked by tribromethanol, a narcotic that presumably acts chiefly on the interbrain.

(B) A rich arborization of unmyelinated nerve fibres is known to pass from the tuberal nerve centers to ramify in the neurohypophysis. The posterior pituitary hormone or a substance indistinguishable from it has been shown to be increased in the cerebrospinal fluid after electrical stimulation of the tuber. It has also been shown to be increased in amount in the fluid of animals under emotional excitement. The interbrain has been shown to be the seat of the primitive emotions which are released from their cortical inhibitions by experimentally disconnecting the nerve paths from the frontal cortex. Theoretically animals so decorticated should show an increase of posterior pituitary hormone in the cerebrospinal fluid.

(C) As a working concept it may be assumed: (1) That under emotional stimuli the posterior pituitary becomes discharged through its

of the cat, Langworthy and Richter (Brain, 1930) 53, 178, have traced the autonomic paths for sudorific impulses from the frontal cortex through the diencephalon to the spinal cord.

specific and histologically demonstrable diencephalohypophysial mechanism; (2) that the active principle or a portion of it enters the cerebrospinal fluid whence presumably by diffusion through the ependyma it may come to act upon diencephalic nuclei for the parasympathetic apparatus; (3) that conditions may conceivably arise when posterior pituitary hormone is discharged into the fluid in sufficient strength to call forth a parasympathetic (cranial autonomic) response as diffuse in its character as is the response on the part of the sympathetic system brought about by the discharge of adrenalin. The neuro-hypophysis, in short, may conceivably bear a somewhat similar relation to the parasympathetic division that the adrenal medulla does to the sympathetic division of the autonomic nervous system.

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